Department of Health

A summary of the health harms of drugs

Technical document

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August 2011

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About this document
This technical report accompanies 'A summary of the health harms of drugs: Final report'. It includes a summary of the main methodological aspects of the work, a series of evidence tables summarising data from the articles identified through the literature searches, and reference details of the literature used to produce the updated tables.

Contents

PART ONE
METHODS

A summary of the health harms of drugs

1. Methods

The methods developed to update the tables from the 2003 report were based on the systematic retrieval and collection of relevant peer reviewed literature. In addition, a lead expert for each licit and illicit drug was designated from within the research team. Alongside the senior researcher and research assistants, the lead expert reviewed the evidence and guided the update of the tables for their relevant areas.

1.1 Literature retrieval

A search strategy was developed for searching electronic sources and relevant websites. Searches were undertaken in MEDLINE, PsycINFO and TOXLINE. Key reports, monographs and reference sources suggested by the lead experts were also used to identify relevant articles and evidence of the health harms of licit and illicit substances.

1.2 Review of new evidence

Study selection proceeded in two phases. In the first stage, titles and abstracts were screened by the research team to identify potentially relevant references. Full text copies of references identified as potentially relevant in phase one were examined further by the lead researcher to determine whether they met the criteria described below. For substances included in the 2003 report, only articles published since 2003 were eligible for inclusion. For any new drugs considered for the update, inclusion of articles was not limited according to the date of publication. Data from articles meeting the inclusion criteria were extracted by the research team onto a standardised form to record concisely, details about the study methods, participants and findings.

1.3 Inclusion and exclusion criteria

Type of population

Studies that included users of licit and illicit drugs in the UK or from countries outside the UK[a] were eligible for inclusion. Animal studies or studies using non-drug-using volunteers enrolled in prospective research were generally excluded, but where a lack of evidence was available from drug using populations, evidence from such studies has been included.

Type of exposure

The list of drugs to be included in the update was agreed between the research team, NTA and DH and included:

- Alcohol
- Amphetamines and amphetamine-type stimulants (amphetamine sulphate, methamphetamine, MDMA ['ecstasy'] and analogues)
- Anabolic agents (anabolic-androgenic steroids, growth hormone, clenbuterol, [human and non-human] chorionic gonadotropin [hCG]2)

[a]Limited primarily to evidence from OECD countries (i.e. Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States)

- Cannabis
- Classical hallucinogens (LSD, psilocybin, mescaline, dimethyltryptamine [DMT])
- Cocaine powder (cocaine hydrochloride) and freebase cocaine (crack/rock cocaine)
- Dissociative anaesthetics (ketamine, phencyclidine [PCP])
- Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL)
- Nitrites (amyl nitrite, butyl nitrite and isobutyl nitrite)
- Novel synthetic drugs
  - Cannabinoids ('Spice')
  - Cathinones (4-methylmethcathinone [4-MMC], mephedrone, methylenedioxypyrovalerone [MDPV], naphyrone, pyrovalerone)
  - Piperazines (benzylpiperazine [BZP], metachlorophenylpiperazine [mCPP], trifluoromethylphenylpiperazine [TFMPP])
  - 2C series phenethylamines (2C-B and related compounds)
  - Tryptamines (5-MeO-DMT and related compounds)
  - Other ('Bromo-dragonFLY')
- Opioids
  - Illicit opioids (heroin)
  - Prescription opioids (methadone, tramadol, dihydrocodeine, oxycodone)
- Over-the-counter products
  - Dextromethorphan
  - Codeine containing products (co-proxamol, co-codamol)
- Plant/herbal products
  - Khat (Catha edulis Forsk)
  - Salvia divinorum
- Prescription drugs
  - Benzodiazepines (temazepam, diazepam, nitrazepam, clonazepam)
  - Non-benzodiazepine hypnotics (zaleplon, zolpidem, zopiclone)
  - CNS stimulants (dexamphetamine, methylphenidate, modafinil)
- Tobacco
- Volatile substances (glues, thinners, aerosols, paints and lighter fuel).

Type of outcome

Studies that examined acute and/or chronic health harms arising from licit and illicit substance use and misuse, including physical (mortality and morbidity) harms, psychological/psychiatric harms, and those relating to dependence, tolerance and withdrawal, were eligible for inclusion. Studies that only reported on surrogate measures of harm (e.g. neuroimaging studies) were excluded.

Type of studies

Evidence from a wide range of sources was eligible for inclusion in the updated tables; however, evidence from systematic reviews and well-designed observational studies (including cohort studies,

case-control studies and cross-sectional studies) was prioritised for inclusion. For drugs[b] where there was a limited evidence base, fatal and non-fatal acute harms identified in case reports and case series have also been collated.

1.3 The updated tables

New evidence identified from the articles retrieved through the literature searches was used to update the evidence presented in the 2003 report. The basic layout of the tables follows the 'framework for typology of dangerousness of drugs' as outlined in the 2003 report, focusing on the acute and chronic problems associated with each substance and factors that mediate or moderate the risk.

Following the format of the 2003 report, evidence on specific harms associated with different contextual factors related to drug use (different routes of administration, polypharmacy, and age and gender-related factors) have been included in the updated tables for each specific drug, and as a set of new tables addressing these as cross-cutting themes across the included substances. Two additional tables also consider the potential health risks arising from adulterants drawing on recent research conducted by the team[1,2].

[b]Dissociative anaesthetics, hallucinogens, novel synthetic drugs, nitrites, khat and salvia divinorum

PART TWO
SUMMARY OF COHORT, CASE-CONTROL AND CROSS-SECTIONAL STUDIES

1. Amphetamines

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Degenhardt et al., (2007)[3] Australia Victoria Adolescent Health Cohort Study Cohort study	1,943 adolescents (14-15 years) recruited from secondary schools in Victoria; 78% followed up Sex: 49% male Age: 14-15 years Ethnicity: NR Substance use: cannabis, tobacco, alcohol	Baseline survey: 14-15 years Follow-up: 11 years Methods: self-report questionnaire Measure(s): amphetamine use; alcohol consumption/ dependence; tobacco use; cannabis use/dependence; Clinical Interview Schedule (CIS-R); Self Report of Early Delinquency Scale; educational, occupational and social measures; Standardised Assessment of Personality; General Health Questionnaire Potential confounders/covariates: other drug use; mental health	Adolescent amphetamine use (age 15-17 years) was associated with poor mental health and cannabis use. By young adulthood (age 24-25 years), adolescent amphetamine users were more likely to meet criteria for dependence upon a range of drugs, to have greater psychological morbidity and to have some limitations in educational attainment. Most of these associations were not sustained after adjustment for early-onset cannabis use
Ito et al., (2009)[4] USA Case-control study	59 adults (>49 years) who were discharged with a primary diagnosis of either cardiomyopathy or heart failure and had a transthoracic echocardiogram performed during hospitalization Sex: 64% male Age: mean 38 years Ethnicity: 48% Pacific Islanders Substance use: 48% used methamphetamine; 12% cocaine; 17% alcohol; 10% cannabis; 32% tobacco	Baseline survey: hospitalised between January 2002 and June 2004 Follow-up: NA Methods: comparison of echocardiams between amphetamine and non-amphetamine using participants Measure(s): left ventricular volume; left atrial volume; transmitral flow velocity; left ventricular ejection fraction; left ventricular mass Potential confounders/covariates: age, gender, cardiac risk factors	Methamphetamine abusers were found to have a more severe form of dilated cardiomyopathy compared with non-abusers. Patients who abused methamphetamine had larger left ventricular end-diastolic volume (LVEDV), end-systolic volume, LAV, right ventricular dimensions, and lower LVEF than patients who did not abuse methamphetamine
Kinner & Degenhardt (2008)[5] Australia Cross-sectional study	750 regular and current ecstasy users who participated in the 2006 Ecstasy and related Drug Reporting System Sex: NR Age: NR Ethnicity: NR Substance use: 81% reported recent use of methamphetamine	Baseline survey: 2006 Follow-up: NA Methods: quantitative survey Measure(s): demographic data including patterns of lifetime and recent use, and some risk-taking items; methamphetamine dependence assessed using the Severity of Dependence Scale (SDS) Potential confounders/covariates:	Compared with participants who had used only other forms of methamphetamine, recent crystal methamphetamine users were more likely to have 'binged' on drugs for ≥48 hours. Non-smoking crystal methamphetamine users (n=78) more often reported recent injecting and heroin use. Recent smokers were more likely to report greater polydrug use, to have recently overdosed on a 'party drug', and have accessed medical services for their drug use. However, many of these associations were accounted for by their injecting and heavier frequency of methamphetamine use

1. Amphetamines

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
McKetin et al., (2006)[6] Australia Cross-sectional study	309 methamphetamine users recruited through advertisements in free-press publications, newspapers, websites, needle and syringe programmes and through word of mouth. Sex: 59% male Age: median 28 years (range 16-60 years) Ethnicity: NR Substance use: methamphetamine use in the past year (100%)	Baseline survey: NR Follow-up: NA Methods: questionnaire/ interview Measure(s): life-time, past-year and past-month use of all major drug types; days of drug use; frequency of injection. Route of methamphetamine administration; frequency of methamphetamine use; methamphetamine dependence. Potential confounders/covariates:	13% of participants screened positive for psychosis in the past year and 23% had experienced clinically significant suspiciousness, unusual thought content or hallucinations during this period. Participants who had experienced a clinically significant symptom of psychosis in the past year were more likely to be dependent methamphetamine users, who took the drug more than weekly, and who had a history of a psychotic disorder. After adjusting for methamphetamine dependence, there was no longer a significant relationship between having had a clinically significant symptom of psychosis in the past year and frequency of methamphetamine use during this time. Dependent methamphetamine users were three times more likely than non-dependent methamphetamine users to experience a clinically significant psychotic symptom in the past year, even after adjusting for a self-reported diagnosis of schizophrenia and other psychotic disorders
Moon et al., (2007)[7] South Korea Cross-sectional study	37 males included 19 diagnosed as methamphetamine dependent and 18 controls Sex: 100% male Age: NR Ethnicity: NR Substance use: average period of methamphetamine use=12.84 years; average drug period was 1.79 years	Baseline survey: NR Follow-up: NA Methods: memory tests administered Measure(s): verbal memory: K-AVLT; and visual memory: K-CFT Potential confounders/covariates: age	A weak significant relationship was found between group and visual memory - methamphetamine use seemed to impair visual memory. No relationship was identified between group and verbal memory
Newton et al., (2004)[8] USA Cross-sectional study	19 non-treatment seeking methamphetamine dependent subjects (26-49 years) who used at least 0.5 grams methamphetamines a week for the 6 months prior to the study and produced a positive methamphetamine sample. Two groups examined; one group was hospitalised (early study entry) and the second group were outpatients (late study entry) Sex: 79% male Age: early study entry group=mean 33.4 years; late study entry group=mean 36.2 year Ethnicity: 58% White; 21% African American; 21% Hispanic Methamphetamine use: early study entry group=mean 20.5 days/month; late study entry group=mean 8.4 days/months	Baseline survey: NR Follow-up: NA Methods: neurocognitive measures Measure(s): Structured Clinical Interview for DSM-IV; Addiction Severity Index; North American Adult Reading Test; Beck Depression Inventory Potential confounders/covariates: NR	Moderate levels of depression were reported during the first days of abstinence with minimal levels reported after. The most prominent symptoms of depression reported were anhedonia, irritability and poor concentration

1. Amphetamines

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Rendell et al., (2009)[9] Australia Cross-sectional study	20 adults with confirmed history of methamphetamine dependence (clinical diagnosis of dependence according to DSM-IV but currently abstinent) and a control group of 20 participants with no self-reported history of substance abuse. Sex: 60% male Age: mean MA 27.5; con 28.2 Ethnicity: Substance use: previous period of methamphetamine use: mean 3.85 years (SD 2.16; range 1-8 years)	Baseline survey: not reported Follow-up: NA Methods: Laboratory measures Measure(s): Hospital Anxiety Depression Scale; National Adult Reading Test; two measures of executive functioning (Phonemic fluency/Hayling Sentence Completion Test); Rey Auditory Verbal Learning Test; Virtual Week measure of prospective memory Potential confounders/covariates: Level of English, years of education, self-rated health, self-rated sleep, other substance use	Methamphetamine use associated with significantly increased prospective memory difficulties
Srisurapanont et al., (2003)[10] Australia, Japan, the Philippines & Thailand. WHO Amphetamine-Type Stimulant (ATS) Project Ecological study	168 in-patient psychiatric patients hospitalised in Australia, Japan, the Philippines and Thailand Sex: 76% male Age: mean 27 years Ethnicity: NR Substance use: age at first methamphetamine use = mean 20 years	Baseline survey: Follow-up: NA Methods: clinical interview Measure(s): Mini-International Neuropsychiatric Interview-Plus (MINI-Plus), Module M. Potential confounders/covariates:	In lifetime, persecutory delusion was the most common symptom (77.4%). Other common symptoms in lifetime were auditory hallucinations, strange or unusual beliefs, and thought reading. Auditory hallucinations were the most common current symptom (44.6%). Current symptoms frequently found were strange or unusual beliefs and visual hallucinations. Current negative symptoms were also found in 36 patients (21.4%). Delusions and hallucinations were the two most severe symptoms during the week prior to assessment.
Westover & Nakonezny (2010)[11] USA Case-control study	30,922,098 individuals aged 18-49 years with information recorded in a national inpatient administrative database (Healthcare Cost and Utilization Project Nationwide Inpatient Sample) Sex: NR Age: 18-49 years Ethnicity: NR Substance use: active amphetamine abuse or dependence identified (including methamphetamine, amphetamine, and ecstasy)	Baseline survey: hospitalisation from January 1995-December 2007 Follow-up: NA Methods: retrospective review of primary and secondary discharge diagnoses for aortic dissection Measure(s): ICD-9-CM codes for aortic dissection Potential confounders/covariates: age, cocaine use, hypertension, smoking, heredity vascular diseases, dyslipidemia, connective tissue disorders, vascular inflammation, trauma and Turner syndrome	When controlling for known risk factors, amphetamine abuse/dependence was significantly associated with aortic dissection (adjusted odds ratio 3.33, 95% CI 2.37-4.69). Amphetamine abuse/dependence accounted for 0.76% of all aortic dissections between 1995 and 2007

2. MDMA and analogues

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
de Win et al., (2006)[12] Netherlands XTC Toxicity study Cohort study	188 ecstasy-naive young adults (18-35 years old) with high probability for future ecstasy use; 64% followed up (59 incident ecstasy users and 61 persistently ecstasy naive participants) Sex: 41% male Age: mean 21.7 years Ethnicity: NR Substance use: Similar levels between groups for alcohol, tobacco, cocaine and amphetamine use, but incident ecstasy users had higher cannabis use than ecstasy naive controls at baseline	Baseline survey: 2002-2003 Follow-up: 12-24 months Methods: self-reported survey Measure(s): Beck Depression Inventory; Barratt Impulsiveness Scale; and American Sensation Seeking Scale (Dutch version) Potential confounders/covariates: lifetime ecstasy use and last year use of alcohol, tobacco, cannabis, amphetamines and cocaine; verbal intelligence	After adjustment, a statistically significant effect of ecstasy use was observed on certain aspects of sensation seeking. No effect of ecstasy use on depression or impulsivity
Falck et al. (2008)[13] USA Cohort study	402 young adults (18-30 years old) resident in Ohio, USA who had used MDMA at least once in the past six months; 73% followed up at 24 months. Sex: 64% male Age: mean 21 years Ethnicity: 82% White MDMA/'ecstasy' use: mean 36.2 occasions	Baseline survey: 2002-2004 Follow-up: 24 months Methods: self-administered Measure(s):Beck Depression Inventory (BDI-II) Potential confounders: sociodemographic characteristics, frequency of other nonmedical drug use	Participants who had used MDMA on more than 50 occasions had significantly higher scores than those who had used less often. Over follow-up, participants who reported continued use of MDMA had higher scores at baseline and at the 24-month follow-up (significance not reported). Authors note that scores fell into the range suggesting 'no to minimal' depression
Fisk et al., (2009)[14] UK Cross-sectional study	95 'ecstasy'/polydrug users who currently used or who had previously used ecstasy Sex: 56% male Age: mean 22 years Ethnicity: NR Substance use: mean lifetime ecstasy dose = 328 tablets (SD 416); mean frequency of use = 0.39 times per week (SD 0.44)	Baseline survey: 2002-2007 Follow-up: NA Methods: neuropsychological tests Measure(s): Scholastic Aptitude Test analogy quiz; Raven's Progressive Matrices; National Adult Reading Test; computation span; letter updating; plus-minus task; number letter task; Chicago word fluency test; random letter generation task; Everyday Memory Questionnaire; Cognitive Failures Questionnaire; Prospective Memory Questionnaire; Epworth Sleepiness Scale; sleep type indicator; sleep quality; morning tiredness; mood adjective checklist; patterns of drug use Potential confounders/covariates: NR	The majority of the sample indicated that ecstasy use had not changed their behaviour; however, >40% of users reported ecstasy had made them more paranoid and/or less healthy, >30% indicated that ecstasy had made them more moody and/or more irritable, and >20% less patient and/or more confused. There was no significant relationship between the number of reported adverse ecstasy-related effects and the amount illicit drugs consumed during the previous 10 days. Measures of intelligence, including emotional intelligence, were significantly and negatively related to the reported number of adverse reactions associated with ecstasy use. None of the measures of executive functioning were significantly associated with the number of reported adverse reactions. Adverse reactions to ecstasy were significantly associated with short-term prospective memory problems and sleep problems. Those reporting more adverse effects were subject to impaired sleep and increased daytime tiredness
Gouzoulis-Mayfrank et al. (2005)[15] Germany Cohort study	60 MDMA users who had used the drug on at least 20 occasions; 63% followed up (n=17 interim users* and n=21 continuing users**) Sex: 71% male Age: NR Ethnicity: NR Substance use: NR	Baseline survey: NR Follow-up: 18 months Methods: battery of working memory and memory tests Measure(s): Digit Span backwards from the revised form of the WAIS; 2-back from the Test for Attentional Performance; LGT-3 (learning and memory test). Potential confounders/covariates: NR	Performance on the memory tests remained stable over the follow-up period in the interim users and did not change in the continuing users

2. MDMA and analogues

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Halpern et al., (2011)[16] USA Cross-sectional study	111 participants (18-45 years) who reported (1) at least 17 life-time episodes of ecstasy use (n=52) or (2) no life-time ecstasy use (n=59); participants were required to report experiences of 'rave culture' (having attended at least 10 all-night dance parties) Sex: 61% male Age: median 22-24 years across groups Ethnicity: 85% White Substance use: life-time alcohol intoxications = 20; life-time cannabis intoxications = 11	Baseline survey: NR Follow-up: NA Methods: neuropsychological testing Measure(s): Wechsler Adult Intelligence Scale, revised; Rey-Osterreith Complex Figure Test; Wisconsin Card Sorting Test; Reitan Battery; Raven's Progressive Matrices; Benton Controlled Verbal Fluency Task; Stroop Test; California Verbal Learning Test, 2nd edition; Wechsler Memory Scale, 3rd edition; Revised Strategy Applications Test (RSAT); Iowa Gambling Task; Grooved Pegboard Test; Beck Depression Inventory Potential confounders/covariates: age; gender; race/ethnicity; four family-of-origin variables; history of childhood conduct disorder; and childhood ADHD	Few differences reaching statistical significance were found when the authors compared the overall group of users with non-users on the entire range of neuropsychological tests, or when 'moderate' and 'heavy' user subgroups were compared with non-users. Ecstasy users exhibited lower vocabulary scores on the RSAT than non-users, however the authors report that this finding probably indicates differences in pre-morbid ability rather than neurotoxicity of ecstasy
Hoshi et al., (2007)[17] UK Cross-sectional study	109 participants (25-50 years) including 25 current ecstasy users (at least monthly use and on at least 25 occasions); 28 ex-users (used ecstasy on at least 25 occasions but not in the last year); 29 polydrug users (used a range of other recreational drugs but had never taken ecstasy); and 27 drug-naïve controls who had no history of drug use, apart from alcohol Sex: NR Age: 25-50 years Ethnicity: NR Substance use: see study population details	Baseline survey: NR Follow-up: NA Methods: cognitive assessment; mood assessment Measure(s): immediate and delayed prose recall; Buschke Selective Reminding task; Go/No-go task; Rapid visual information processing; Serial Sevens task; Semantic and phonemic verbal fluency; Trail Making Test; CANTAB spatial working memory; CANTAB Stockings of Cambridge; Gibson's spiral maze; Barratt Impulsiveness Scale; and the Aggression Questionnaire Potential confounders/covariates: impulsivity score and the time since cannabis, cocaine and amphetamines	Participants in all three drug using groups showed a 'general tendency' towards impaired learning and recall of verbal memory. Some evidence of impaired response inhibition among current ecstasy users and polydrug users. No other group differences were observed
Jager et al. (2007)[18] Netherlands XTC Toxicity study Cohort study	96 ecstasy-naive young adults (18-35 years old) with high probability for future ecstasy use; 51% followed up (n=25 novice ecstasy users and n=24 control participants) Sex: 41% male Age: mean 22 years Ethnicity: NR MDMA/ecstasy use: not applicable	Baseline survey: 2002-03 Follow-up: approx. 18 months Methods: fMRI scanning Measure(s): working memory task based on Sternberg's item-recognition paradigm; visuo-auditory selective attention task; and a pictorial associative memory task Potential confounders: lifetime and last year use of cannabis, amphetamine, cocaine and last year alcohol and tobacco consumption; demographic variables (age, gender, and verbal IQ)	There was no evidence of the sustained effects of initial ecstasy use on task performance in the domains of memory and attention. There was no effect of incident ecstasy use on brain activity in the brain systems engaged in working memory, attention, or associative memory

2. MDMA and analogues

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Matthews & Bruno (2010)[19] Australia Cross-sectional study	100 participants who had used ecstasy at least monthly in the preceding 6 months (at least 16 years of age) Sex: 54% male Age: median 23 years (range 17-40 years) Ethnicity: NR MDMA/ecstasy use: median 12 days in preceding 6 months (range 6-100 days); median 2 tablets taken in typical session (range 1-7 tablets)	Baseline survey: May and August 2007 Follow-up: NA Methods: structured interviews Measure(s): patterns of ecstasy and other drug use; nature and incidence of risk behaviours and health harms associated with drug use; Center for Epidemiological Studies Depression Scale; Kessler Psychological Distress Scale; mental health problems during the previous 6 months Potential confounders/covariates: demographic characteristics and other drug use	28% of the sample had a score indicating high levels of depression, and 15% of the sample had scores indicative of a possible diagnosis of an anxiety or affective disorder. 35% of the sample self-reported a mental health problem during the previous 6 months (most commonly depression and/or anxiety). Recent injecting drug use, self-reported psychological ecstasy dependence (SDS), consuming 2 or more pills on a typical occasion of ecstasy use, and engaging in harmful alcohol consumption (AUDIT score ≥16) were found to be the most significant predictors of depressive symptoms
Parrott et al., (2006)[20] UK Cross-sectional study	206 ecstasy users; 56% moderate users (10-99 lifetime occasions), 27% novice (<10 occasions) and 17% heavy user (100+ occasions) Sex: 60% male Age: NR Ethnicity: NR Substance use: see population details	Baseline survey: NR Follow-up: NA Methods: prospective memory and ecstasy use examined Measure(s): Prospective Memory Questionnaire (PMQ) UEL Recreational Drug Use Questionnaire. Potential confounders/covariates: NR	Results suggested an association with overheating and memory problems: Those who danced 'all the time' when on ecstasy, reported significantly more PMQ memory problems than less intensive dancers. Prolonged dancing was also associated with more complaints of depression, memory problems, concentration and organizational difficulties afterwards. Feeling hot when on ecstasy was associated with poor concentration in the comedown period, and with mood fluctuation and impulsivity off-drug. PMQ long-term problems demonstrated a significant relationship with thermal self-ratings. More memory problems were noted by those who felt very hot, and by those who did not feel hot when on ecstasy
Schilt et al. (2007)[21] Netherlands XTC Toxicity study Cohort study	188 ecstasy-naive young adults (18-35 years old) with high probability for future ecstasy use; 63% followed up (n=58 incident ecstasy users and n=60 persistently ecstasy naive participants) Sex: 41% male Age: mean 22 years Ethnicity: NR MDMA/ecstasy use: not applicable	Baseline survey: 2002-2003 Follow-up: mean 17 months Methods: neuropsychological tests Measure(s): Paced Auditory Serial Addition Test; Rey Auditory Verbal Learning Test (Dutch version); Memory for Designs test; and Mental Rotation Task Potential confounders: substance use other than ecstasy (alcohol, tobacco, cannabis, amphetamines and cocaine); verbal intelligence	After controlling for the use of other substances, there was a statistically significant difference in verbal memory performance among ecstasy users compared to persistently ecstasy-naive participants. No differences between the two groups were observed on other neurocognitive tests
Scott et al., (2010)[22] Australia Cross-sectional study	Community sample of 184 individuals (18-35 years old) who had taken ecstasy at least once in the last 12 months. 184 Sex: 47% male Age: mean 23.3 years Ethnicity: 72% white, 7% Asian, 6% Indian, 5% mixed, 1% indigenous Australian Substance use: mean duration ecstasy use 4.2 years (SD 3.6 years); lifetime ecstasy use mean 172.4 pills (SD 507.4)	Baseline survey: NR Follow-up: NA Methods: interview, questionnaire and saliva sample Measure(s): substance use, mood symptoms, serotonin transporter, trauma (Composite International Diagnostic Interview – Trauma List), life stress Potential confounders/covariates: demographic, genetic and environmental risk factors, including other drug use	Lifetime and recent ecstasy use were not associated with the level of current depressive and/or anxiety symptomatology. Recent polydrug use was a significant predictor of general distress anxiety symptoms with participants who had taken a greater number of drugs in the preceding 28 days reporting more severe current anxiety symptoms

2. MDMA and analogues

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
ter Bogt & Engels (2005)[23] The Netherlands Cross-sectional study	490 participants attending four parties, 372 (77%) of whom had lifetime use of MDMA. Of that 372, 60% had used MDMA that night. Within the group of users, 85% used MDMA in the past month, 30% used once a month, 26% a few times a month, 17% weekly, 11% more than weekly Sex: 66% male Age: mean 22.3 years Ethnicity: NR Substance use: monthly use of cannabis (74%); psilocybin (15%); speed (27%); cocaine (36%)	Baseline survey: 2001-2002 Follow-up: NA Methods: Association of MDMA use and psychosocial effects examined Measure(s): Substance use; motives to use drugs; energy; euphoria; self-insight; sociability, sexiness; coping, conformism; perceived positive effects; perceived negative effects Potential confounders/covariates:	66% of the partygoers reported they had ever experienced depression. Confusion (63%) and being out of control (61%) were also common negative effects. Lower in the hierarchy stood the effects of nausea (50%), suspiciousness (50%), edginess (46%), and dizziness (46%). Less often perceived negative effects were aggression (34%), fear (38%), and headache (39%) and fainting (21%). Women tended to experience more depression, nausea, dizziness, and headache, and they were more susceptible to feeling faint or actually fainting. Women were more fearsome and tended to rate themselves more easily out of control and aggressive. Participants who indulged in polydrug use also reported to experiencing stronger negative effects
Thomasius et al., (2005)[24] Germany Cross-sectional study	120 participants; n=30 current ecstasy users (regular use for 20 weeks), n=31 ex-ecstasy users (minimum 250 tablets but ecstasy free for 20 weeks), n=29 poly-drug controls and n=30 drug-naive controls Sex: 51% male Age: mean 24 years Ethnicity: NR Substance use: (see participant details for ecstasy use). Mean grams of cannabis in past year: ecstasy users=88g, ex-users=281g, controls=142g. Mean grams cocaine in past year: ecstasy users=6g, ex-users=5g, controls=16g. Amphetamine / ecstasy users=15, ex users=9, controls=1. LSD use times: ecstasy users=22, ex-users=27, controls=11	Baseline survey: NR Follow-up: NA Methods: association of ecstasy use and prevalence of mental disorders examined Measure(s): Diagnostic and Statistical Manual version IV (DSM-IV) - mental disorders Potential confounders/covariates: NR	Substance-induced affective, anxiety and cognitive disorders occurred more frequently among ecstasy users than polydrug controls. The life-time prevalence of ecstasy dependence amounted to 73% in the ecstasy user groups. More than half of the former ecstasy users and nearly half of the current ecstasy users met the criteria of substance-induced cognitive disorders at the time of testing. Logistic regression analyses showed the estimated life-time doses of ecstasy to be predictive of cognitive disorders, both current and lifetime
Zakzanis & Campbell (2006)[25] Canada Cohort study	15 current and former MDMA users; 100% followed up (n=7 current users and n=8 former users) Sex: 80% male Age: range 17-31 years Ethnicity: not reported MDMA/ecstasy use: not reported	Baseline survey: NR Follow-up: 24 months Methods: neuropsychological tests Measure(s): WAIS III Vocabulary and Block Design subtests; and Rivermead Behavioral Memory Test Potential confounders: NA	Test scores declined among current users and remained static or improved among former users. Authors note that as there was a significant age difference between current and former users (mean 29 years vs. mean 20 years) statistical tests were not performed between groups

3. Anabolic agents

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Graham et al., (2006)[26] UK Cross-sectional study	40 participants divided into 4 groups: AAS users (mean age 42.4 years); AAS users abstinent for 3 months (mean age 41.7 years); non-drug using bodybuilding controls (mean age 43.1 years); sedentary male controls (mean age 43.8 years); Sex: 100% male Age: mean 42 to 44 years across groups Ethnicity: NR Substance use: see participant details	Baseline survey: NR Follow-up: NA Methods: steroid use and homocysteine blood plasma levels examined Measure(s): levels of homocysteine, testosterone, weight Potential confounders/covariates: NR	Plasma concentrations of homocysteine were significantly higher in the user group than the abstinent group or either control group
Larance et al., (2008)[27] Australia Cross-sectional study	60 participants (17 years and older) and had used anabolic substances (anabolic–androgenic steroids, human growth hormone or insulin-like growth factors) for non-medical purposes in the preceding 6 months Sex: 100% male Age: mean 32 years Ethnicity: NR Number of PIED cycles in past year: median 2 (range 1-4); median cycle length = 10 weeks; concurrent use of more than one AAS product in the most recent cycle was common; 93% had ever injected PIEDs	Baseline survey: January-August 2005 Follow-up: NA Methods: structured face-to-face interviews Measure(s): patterns of use; injecting behaviour; BBV status Potential confounders/covariates: NR	Low rates of needle sharing among participants (5%); a larger proportion reported reusing needles (13%). 41% of those who had injected PIEDs reported experiencing at least one injection-related problem in the last month (persistent soreness/redness at the site [n=18], scarring/hard lumps [n=5], hitting a vein or persistent bleeding [n=3], swelling of the arm or leg [n=3], abscesses [n=2] and nausea [n=1]). 76% of the sample used illicit drugs, most commonly ecstasy, methamphetamine, cocaine and cannabis, with 27% reporting having ever injected an illicit drug. Self-reports of BBV status were 3% HBV positive, 5% HCV positive and 12% HIV positive
Pagonis et al., (2006)[28] Greece Cohort study	320 body-building, amateur and recreational athletes (19-43 years old); n=160 AAS users, n=80 using placebo compounds and n=80 abstaining from any substance abuse Sex: 64% male Age: mean 28 years Ethnicity: NR Substance use: AAS abuse: heavy use n=73; medium use n=50; light use n=28; no use n=160	Baseline survey: The day before the individual's AAS cycle began Follow-up: 13 months Methods: psychopathological factors measured at three points during the individual's AAS use cycle Measure(s): System Check List-90; Hostility and Direction of Hostility Questionnaire Potential confounders/covariates: NR	Evaluation demonstrated a statistically significant increase in all subscales of the SCL-90 and HDHQ for AAS users, while the non-user groups remained stable. Psychiatric and psychological side effects including hostility and aggression are most likely amongst heavy AAS users

4. Cannabis

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Blows et al., (2005)[29] New Zealand Case-control study	1,317 participants involved in accidents where one vehicle occupant was hospitalised with injuries, or killed; 746 controls (mean age 40.8 years) from vehicles identified at random Sex: cases=65% male; controls=59% male Age: case=mean 37 years; controls=mean 41 years Ethnicity: white/European (65%); Maori (15%); Pacific islander (11%); other (9%) Substance use: cannabis; alcohol	Baseline survey: March 1998-July 1999 Follow-up: NA Methods: The relationship between cannabis use and car accidents investigated by comparing cannabis use in persons who had been in a vehicle accidents with controls Measure(s): Cannabis use: acute use in past 3 hours; habitual use (less than once a week, once a week or more); Stanford sleepiness score; time of day, number of passengers, age of vehicle. Risky driving behaviours: seat belt use; blood alcohol concentration; seat belt use Potential confounders/covariates: time of day, sleepiness, age, education level, gender, driving exposure, age of vehicle	Acute cannabis use in the 3 hours prior to driving was associated with car crash injury and remained significant after controlling for confounders (age, education, driving exposure, age of vehicle, number of passengers). After controlling for confounders and risky driving behaviours at time of crash there was no significant association however between acute cannabis use and car crash injury. Association between habitual cannabis use (past 12 months use) and car crash injury was significant after controlling for all confounders and risky driving behaviours at time of crash and acute cannabis use
Fried et al., (2005)[30] Canada Ottawa Prenatal Prospective Study Cohort study	121 current light and heavy users of cannabis n=59 did not use cannabis and made up the control group. Current light users (n=19), current heavy users (n=19) and former users (n=16) made up the comparison groups.; 113 Sex: 56% male Age: 17-21 years old Ethnicity: NR Substance use: 10 out of 113 had tried cannabis at baseline	Baseline survey: Follow-up: at 17-21 years Methods: cognitive tests Measure(s): Weschler Adult Intelligence Scale; Peabody Picture Vocabulary; Weschler Memory Scale 3rd edition; Test of Variables of Attention; Adult Category Test Potential confounders/covariates: SES variables; maternal use of alcohol, cigarettes, and cannabis use during pregnancy; age and sex; young adult's cigarette and alcohol use; DSM positive criteria for DSM-IV Axis I disorders (generalized anxiety, major depression, dysthymic disorder, attention deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, alcohol dependence and abuse)	After controlling for pre-use performance the heavy use group, in comparison to controls, had lower mean scores in Immediate and delayed memory, Processing Speed Index and Full Scale IQ. No relationship was found between current cannabis use and the Working Memory, Verbal IQ, Peabody Picture Vocabulary Test, the Adult Category Test or the Test of Variables of Attention tasks. No significant differences in performance were found between former users and controls
Gerberich et al., (2003)[31] USA Cross-sectional study	64,657 members of the Kaiser Permanente Medical Care Program (15-49 years) who completed multiphasic health checkups from 1979-1985 Sex: 43% male Age: mean 33 years Ethnicity: 28% Black; 53% White; 11% Asian; 5% Latino; 3% other Substance use: 22% current cannabis users; 20% former cannabis users; 59% non-cannabis users. The majority were occasional alcohol users and non-smokers	Baseline survey: 1979-1985 Follow-up: NA Methods: hospitalisation Measure(s): times hospitalised Potential confounders/covariates: alcohol use; age; cigarette use, medical conditions	Increased all-cause injury hospitalizations for both men and women among current users relative to nonusers (adjusted for age, cigarette, medical conditions and alcohol use) Increased rates of motor vehicle assault and self-inflicted injuries were identified among men who were current users Increased rate of self-inflicted injuries in women who were current users

4. Cannabis

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Kuepper et al., (2011)[32] Early Developmental Stages of Psychopathology study Germany Cohort study	Analysis of 1,923 participants (aged 14-24 years) who completed the T3 assessment of the EDSP study and provided complete information on substance use and psychotic symptoms Sex: 48% male Age: mean 18 years at baseline; mean 27 years at T3 Ethnicity: NR Substance use: 2% reported use of drugs other than cannabis at both baseline and T2	Baseline survey: 1994 Follow-up: T2=3.5 years; T3=8.4 years Methods: clinical interview Measure(s): Munich composite international diagnostic interview Potential confounders/covariates: age at baseline, sex, socioeconomic status, use of other drugs at baseline and T2, childhood trauma, and urban/ rural environment	Lifetime cannabis use (as assessed at T2) significantly increased the risk of psychotic experiences at T3 (adjusted odds ratio 1.5; 95% CI 1.1, 2.1). There was no evidence for self medication effects. There was a significant association between cannabis use at both baseline and T2 and risk of persistence of psychotic experiences (adjusted odds ratio 2.2; 95% CI 1.2, 4.2)
Preuss et al., (2010)[33] Germany Cross-sectional study	118 participants with a diagnosed cannabis dependence according to DSM-IV and seeking planned detoxification Sex: 86% male Age: mean 19.7 years Ethnicity: NR Substance use: NR	Baseline survey: NR Follow-up: NA Methods: semi-structured interview Measure(s): modified German version of the Marijuana Withdrawal Checklist (MWC); German Version of the Structured Clinical Interview for DSM Disorders (SCID I); history of cannabis use; THC urine sample; cigarette smoking Potential confounders/covariates: NR	Most frequently mentioned physical symptoms of strong or very strong intensity on the first day were sleeping problems (20.7%), sweating (28.2%), hot flashes (20.7%) and decreased appetite (15.4%). Large overlap between psychological and physical symptoms: 79.6% with psychological symptoms reported elevated physical symptoms, and 75.4% with physical symptoms reported elevated psychological symptoms. 42.4% reported neither increased physical nor psychological symptoms. Large overlap with craving; 70.8% in the high craving subgroup reported elevated psychological or physical symptoms
Price et al., (2009)[34] Sweden Cohort study	50,087 Swedish men conscripted for military training during 1969-1970 (>98% aged 18-20 years old) Sex: 100% male Age: range 18-20 years Ethnicity: NR Substance use: stimulants (56.2%), opiates (20.4%), other non-prescribed substances (37.2%)	Baseline survey: 1969-1970 Follow-up: at 23-24 years (up to 2003) Methods: suicides and unidentified deaths matched to baseline measures of cannabis use Measure(s): Swedish National Cause of Death Register; frequency of cannabis use and other drug use Potential confounders/covariates: age, family social economic status, parental factors, IQ, tobacco alcohol and other drug use, problem behaviour during childhood, psychological adjustment, social relations: all considered during analysis	Crude analysis suggested cannabis use was associated with increased risk of suicide, primarily in those using cannabis most frequently. The association was not present however after controlling for personal and social factors
Tijssen et al., (2010)[35] Germany Early Developmental Stages of Psychopathology (EDSP) study Cohort study	Subset of EDSP respondents including 1,395 participants (14-17 years) at baseline; 73% (n=1,022) followed up at T3; analyses conducted in a sample of 705 adolescents Sex: male 53% Age: mean 15 years at baseline Ethnicity: NR Substance use: 1.6% regular alcohol use; 4.4% lifetime cannabis use (5+ times)	Baseline survey: 1994 Follow-up: T0-T1=1.6 years; T0-T2=3.4 years; T0-T3=8.3 years Methods: Interviews conducted using the computerized version of the Munich-Composite International Diagnostic Interview Measure(s): mood symptoms and risk factors (family history of mood episodes, negative life events, substance use, ADHD, personality) Potential confounders/covariates: age at baseline, sex, and socioeconomic status	Cannabis use was associated with onset, but not persistence, of manic symptoms. However, cannabis use was not associated with the onset or persistence of depressive symptoms

5. Cocaine and crack cocaine

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Alaraj et al., (2010)[36] USA Case-control study	573 patients with aneurysmal subarachnoid haemorrhage admitted to hospital; cocaine users (n=31) and non-users (n=542) Sex: 31% male Age: cocaine users=45 years; non-users= 54 years Ethnicity: NR Substance use: 5% cocaine, 49% tobacco, 44% used alcohol socially, 11% used alcohol heavily	Baseline survey: June 2002-July 2007 Follow-up: NA Methods: clinical diagnosis Measure(s): cocaine use on clinical toxicology or self-report; all aneurysmal SAH confirmed by computed tomography or lumbar puncture. Potential confounders/covariates: smoking, alcohol use, renal disease, cardiac disease, hypertension, diabetes, hypercholesterolemia	There was no difference between cocaine use and non-cocaine users in unfavourable short-term outcome, incidence of symptomatic or radiologic vasospasm, stroke, or death
Aslibekyan et al., (2008)[37] USA Cross-sectional study	11,993 participants (18-59 years) from annual cross-sectional surveys conducted from 1988 to 1994 Sex: NR Age: 18-59 years Ethnicity: NR Substance use: weighted prevalence of lifetime cocaine exposure 14% (95% CI 12–15%)	Baseline survey: 1988-1994 Follow-up: NA Methods: home interviews, medical examinations, and laboratory tests Measure(s): lifetime cocaine use; lifetime history of myocardial infarction Potential confounders/covariates: age, sex, race, medical insurance status, education, smoking, history of diabetes mellitus, hyperlipidemia and hypertension	There was no statistically significant association between any exposure to cocaine and myocardial infarction. Participants who reported using cocaine >10 times had a 3-fold higher prevalence of myocardial infarction (OR 3.13; 95% CI 0.80-12.25), although the result was not significant. Calculation of the population attributable risk % showed that 10.2% of non-fatal myocardial infarction cases were associated with >10 lifetime occurrences of cocaine use
Bamberg et al., (2009)[38] USA Rule Out Myocardial Ischemia using Computed Assisted Tomography (ROMICAT) study Cross-sectional study	176 patients presenting with acute chest pain; including 44 participants who had used cocaine on greater than 3 times in the past year matched to 132 controls Sex: 86% male Age: mean 46 years Ethnicity: NR Substance use: 50% smokers; 25% cocaine users – 36% intravenous use, 18% concomitant use with other drugs	Baseline survey: NR Follow-up: NA Methods: clinical diagnosis Measure(s): coronary multidetector computed tomography (MDCT) scanning Potential confounders/covariates: smoking, diabetes, hypertension, hyperlipidemia, lipoprotein density	Patients with history of cocaine use had a significantly higher rate of acute coronary syndrome History of cocaine use was not associated with: higher prevalence of any, calcified, or non-calcified plaque or the extent of any, calcified, or non-calcified plaque; prevalence of significant coronary stenosis.
Hsue et al., (2007)[39] USA Case-control study	83 participants had been resuscitated after sudden cardiac death, 22 of whom had used crack cocaine in the previous 24 hours. Controls were resuscitated after cardiac arrest including 41 participants matched on age and 20 un-matched participants Sex: 66% male Age: cocaine users=mean 42 years; un-matched group=mean 68 years; matched group=mean 42 years Ethnicity: African American (47%); other (53%) Substance use: see participant details	Baseline survey: July 2002-February 2003 Follow-up: NA Methods: interviews: injecting behaviours and overdose Measure(s): drug use history, cocaine use history, cocaine dependence and cocaine overdose Potential confounders/covariates: NR	Injecting cocaine users had higher severity of dependence scores and were more likely to be classed as cocaine dependent. In total, 13% of the sample reported overdose on cocaine and 7% in the past 12 months. Injecting cocaine users were significantly more likely to have overdosed than non-injecting users, however there was no significant difference between the proportion of injecting cocaine users and non-injecting users reporting overdose in the past 12 months. Common symptoms reported by those overdosing included palpitations (68%), intense sweating (44%) and seizures (40%), paranoia (32%), severe agitation (32%), respiratory distress (28%), chest pain (28%) and tremors (28%)

5. Cocaine and crack cocaine

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Kaye & Darke (2004)[40] Australia Cross-sectional study	200 participants (18-54 years) who had used cocaine at least once in the past 12 months; 60% classed as injecting cocaine users, 88% of which injected on every occasion Sex: 65% male Age: mean 30 years Ethnicity: NR Substance use: 25% enrolled in methadone maintenance; 6.5% buprenorphine	Baseline survey: July 2002 - February 2003 Follow-up: NA Methods: interviews: injecting behaviours and overdose Measure(s): drug use history, cocaine use history, cocaine dependence and cocaine overdose Potential confounders/covariates: NR	Injecting cocaine users had higher severity of dependence scores and were more likely to be classed as cocaine dependent. 13% of the sample reported overdose on cocaine and 7% in the past 12 months. Injecting cocaine users were significantly more likely to have overdosed than non-injecting users, however there was no significant difference between the proportion of injecting cocaine users and non-injecting users reporting overdose in the past 12 months. Symptoms reported by those overdosing included palpitations (68%), intense sweating (44%) and seizures (40%), paranoia (32%), severe agitation (32%), respiratory distress (28%), chest pain (28%) and tremors (28%)
Kaye & Darke (2004)[41] Australia Cross-sectional study	212 participants (17-51 years) who had used cocaine at least once in the past six months; n=133 (63%) injecting cocaine users (ICUs) and n=79 (37%) non-injecting cocaine users (NICUs) Sex: 68% male Age: mean 29 years Ethnicity: NR Substance use: 34 enrolled in a methadone programme. ICUs: heroin (56%) or cocaine (35%) primary drug of choice. 95% used heroin, 85% cannabis, 62% alcohol. Non ICUs: ecstasy (61%) or cocaine (24%) primary drug of choice. 99% used ecstasy, 96% amphetamines, 91% alcohol	Baseline survey: April - June 2001 Follow-up: NA Methods: interview investigating injecting cocaine and cocaine related dependence and problems Measure(s): physical and psychological problems associated with cocaine use; cocaine dependence Potential confounders/covariates:	A significantly greater proportion of ICU than NICU had experienced at least one severe or chronic cocaine-related physical symptom in the last 12 months. More years of cocaine use, higher frequency of use and higher levels of cocaine dependence were associated with a greater degree of associated harm. The most common physical problems among ICU were severe weight loss (43%), heart palpitations (38%) and chronic insomnia (33%). The most common physical problems among NICU were nasal bleeding or ulceration (19%), chronic sinus/nasal congestion (19%), and heart palpitations (13%). ICU were significantly more likely than NICU to have experienced at least one serious psychological symptom since using cocaine in the last 12 months. More years of cocaine use, higher frequency of use and higher levels of cocaine dependence were associated with a greater degree of physical harm. ICU were more likely than NICU to report paranoia, anxiety, violent behaviour and hallucinations. The most common psychological problems experienced were the same for both ICU and NICU: anxiety, depression and paranoia. A greater number of prior psychological symptoms and higher levels of dependence were associated with a greater severity of current psychological symptoms
Kelley et al., (2005)[42] USA Cross-sectional study	12 patients acutely withdrawing from cocaine recruited from a regional referral inpatient drug recovery program in the community and 12 matched controls Sex: 50% male Age: mean 37 years Ethnicity: withdrawal group: White (75%); African American (17%); multiracial (8%) Substance use: All 12 participants reported cocaine as their primary drug of use. 1 reported opiate use in the past 6 months; 3 had history of heavy alcohol use, regular tobacco use and daily cannabis use	Baseline survey: NR Follow-up: NA Methods: neuropsychological tests Measure(s): Wisconsin Card Sorting Test (WCST) and the anagram task; Controlled Oral Word Association (COWA) test; California Verbal Learning Test, Rey Complex Figure Test, Stroop Test Potential confounders/covariates: IQ, educational level	Impairments were found on the cognitive flexibility tasks. Impairments were also present in verbal fluency and verbal memory, but not spatial memory or attention. Individuals withdrawing from cocaine tended to be impaired on tasks most dependent on verbal ability, including verbal memory (all measures of the CVLT) and verbal fluency (COWA for letters and a trend for animal names). No significant impairment was found on any tasks involving spatial construction or memory (Rey CFT) or some measures of attention (Stroop). All results except for the percentage correct score on the WCST remained significant when covariates for premorbid IQ and educational level were included

5. Cocaine and crack cocaine

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Patkar et al., (2004)[43] USA Cross-sectional study	168 dependent crack cocaine users (min 4g/week), recruited from an outpatient cocaine treatment program; n=86 smoked tobacco; n=48 smoked both tobacco and cannabis; n=34 did not smoke tobacco or cannabis; Sex: 68% male Age: mean 32-36 years across groups Ethnicity: 85% African American; 12% White; 4% Hispanic Substance use: see participant details	Baseline survey: Follow-up: Methods: drug use and physical and psychological symptoms Measure(s): MILCOM self-report questionnaire; Addiction Severity Index; Beck Depression Inventory Potential confounders/covariates: age, mood symptoms	Crack+tobacco+cannabis smoking patients reported the highest number of symptoms; reported the highest number of symptoms on the respiratory, nose-throat, digestive and general subscales Crack only patients reported the highest symptoms on the mood scale (after controlling for age and depression) Regular use of cannabis and tobacco amongst crack users was associated with higher reports of medical symptoms than the use of tobacco alone Amongst crack/tobacco users, a significant positive correlation was obtained between amount of cigarettes smoked and scores on the respiratory and nose—throat scales
Ryb et al., (2009)[44] USA Cohort study	21,500 individuals who had undergone cocaine toxicology testing at the time of admission to trauma centre following injury; Sex: 73% male Age: mean 34 years Ethnicity: White 70%; Black 28%; Others 2% Substance use: 11% tested positive for cocaine; 33% tested positive for alcohol (BAC levels >1 gm/dL)	Baseline survey: on admission to trauma centre Follow-up: 1.5-14.15 years Methods: examined cocaine status on admission in relation to risk of subsequent death by suicide, homicide and unintentional injury Measure(s): tests for blood alcohol concentration and cocaine use; Potential confounders/covariates: age, ethnicity, gender: all controlled for during analysis	Positive cocaine status on trauma centre admission was associated with a lower survival rate because of subsequent homicide and unintentional injury death during the follow-up period. After controlling for admission characteristics, subsequent unintentional injury death, but not subsequent homicide death, was associated with positive cocaine status. Cocaine status was not associated with subsequent suicide
Satran et al., (2005)[45] USA Case-control study	112 participants with a history of cocaine use and coronary angiography recruited over a ten year period at a Medical Centre; n=79 non-cocaine using patients within the same time period were used as controls Sex: 71% male Age: mean 44 years Ethnicity: NR Substance use: Participants were cocaine users. Tobacco use: cocaine users (95%); controls (71%)	Baseline survey: NR Follow-up: NA Methods: angiograms of study and control patients examined Measure(s): angiograms examined for the presence of coronary artery aneurysm and coronary heart disease Potential confounders/covariates: age, sex, race, cardiac risk factors, cardiac events. Similar in controls and participants but higher tobacco use in cocaine use group	Among cocaine users, 34 of 112 (30.4%) had coronary artery aneurysms compared with 6 of 79 (7.6%) in the non-cocaine using control group. The association was significant when cardiac risk factors were controlled for
Story et al., (2008)[46] UK Case-control study	970 pulmonary patients (15-60 years) including crack cocaine users (n=22), other hard drug users (n=115, predominantly heroin, but excluding cannabis and alcohol only) and non-drug users (n=833) Sex: 57% male Age: 15-60 years Ethnicity: 21% White; 39% Black African; 6% Black Caribbean; 27% South Asian; 8% other Substance use: see participant details	Baseline survey: July 2003 Follow-up: NA Methods: diagnosis of tuberculosis Measure(s): sputum smear Potential confounders/covariates: age, ethnicity, drug resistance, ioniazid resistance, sought treatment at emergency department	Crack cocaine users were more likely to be smear positive compared with non-drug users (RR 2.4; 95% CI 2.0-2.9) and drug users not known to use crack cocaine (RR 1.6; 95% CI 1.4-2.0). The risk of smear-positive disease was higher among drug users than among those not known to use drugs (OR 1.9; 95% CI 1.2-3.0) and highest in crack cocaine users (OR 6.6, 95% CI 1.8-24.3)

6. Ketamine

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Dillon et al., (2003)[47] Australia Cross-sectional study	100 ketamine users (19-42 years); 58% had used ketamine 10 or more times and 35% had used ketamine more than 20 times. 26% considered themselves regular ketamine users. Sex: 70% male Age: mean 30 years Ethnicity: NR Substance use: 67% used alcohol at least weekly; 39% cigarette smokers; 99% had used ecstasy; 97% amphetamines; 96% cocaine; 96% cannabis; 89% MDA; 88% LSD; 84% amyl nitrate; 58% benzodiazepines; 35% nitrous oxide; 31% heroin; 25% GHB	Baseline survey: January 1998-October 1999 Follow-up: Methods: semi structured interview: beliefs and experiences Measure(s): physical effects experienced Potential confounders/covariates:	56% of the participants reported having experienced the 'K-hole' (defined as "a place referring to 'where users are' when under the influence of ketamine"). Level of use was significantly associated with having experienced the K-hole with those using 20+ times being significantly more likely to have experience this than those using ten or less times Physical effects usually experienced included inability to speak (30%); inability to move (22%); blurred vision (21%); pyrexia (17%); increased heart rate (17%); temporary paralysis (16%); lack of coordination (14%) Physical effects ever experienced included: lack of coordination (77%); blurred vision (61%); feeling no pain (49%); pyrexia (41%); inability to speak (39%); increased heart rate (38%); nausea and vomiting (27%); temporary paralysis (23%); difficulty breathing (21%) and increased breathing (17%). 20% stated that they had ever experienced severe side effects as a result of ketamine use
Morgan et al., (2009)[48] UK Cross-sectional study	150 participants; n=30 frequent, n=30 infrequent, n=30 ex-ketamine users, n=30 polydrug and n=30 non-drug-using controls Sex: 71% male Age: mean 25-30 years across groups Ethnicity: NR Years of regular ketamine use: frequent= mean 5.03 years; infrequent=mean 3.69 years; ex-users=mean 6.13 years	Baseline survey: 150 Follow-up: NA Methods: neurocognitive assessments Measure(s): Cambridge Automated Neuropsychological Test Assessment Battery; O-LIFE questionnaire, Peter's Delusion Inventory, Dissociative Experiences Scale, Beck Depression Inventory, Spielberger Trait Anxiety Inventory. Potential confounders/covariates: NR	Frequent ketamine use exhibited higher levels of psychopathology (including schizophrenia-like, dissociate and depressive symptoms) compared to the other groups. However, infrequent users also showed evidence of elevated levels of dissociative and schizophrenia-like symptoms and ex-users demonstrated evidence of elevated delusions. Frequent users showed impairments in recognition memory, working memory and planning
Morgan et al., (2010)[49] UK Cohort study	150 participants; frequent ketamine users (>4 times/week, n=30), infrequent ketamine users (< 4 times/week, n=30), ex-ketamine users (abstinent >1 month, n=30), poly-drug users (n=30) and non-drug users (n=30); 80% followed up at 12 months (25 frequent ketamine users, 27 infrequent, 24 abstinent ketamine users, 23 polydrug and 20 non-drug-users) Sex: 55% male Age: mean 26-31 years across groups Ethnicity: NR Number of years of regular ketamine use: frequent = mean 6.67 years; infrequent= mean 4.69 years; abstinent users=6.89 years	Baseline survey: NR Follow-up: 12 months Methods: semi-structured interview; quantitative assessments of neurocognitive function and psychological wellbeing Measure(s): Cambridge Automated Neuropsychological Test Assessment Battery; Short O-LIFE questionnaire; Peter's Delusion Inventor; Dissociative Experiences Scale; Beck Depression Inventory; Life Events Scale Potential confounders/covariates: alcohol use and IQ data	Among frequent ketamine users there was evidence of cognitive deficits in spatial working memory and pattern recognition memory, and a trend for poorer performance in verbal recognition memory. Evidence of a dose-response effect on delusional symptomatology; frequent users scored highest followed by infrequent users and abstinent users. Evidence of greater dissociative symptomatology among frequent users than the non-drug group. Apparent decrease in schizotypal symptom scores across all groups, with the exception of the frequent ketamine user groups. Depressive symptoms increased in both frequent and abstinent ketamine users

7. Gamma-hydroxybutyrate and gamma-butyrolactone*

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Bell & Collins (2010)[50] UK Cross-sectional study	19 patients attending a specialist 'party drugs' clinic for treatment of GBL dependence Sex: 90% male Age: mean 28 years Ethnicity: NR Substance use: All reported using 'round the clock': 12–40 ml of GBL daily. Three patients had a history of alcohol dependence and one patient was a long term drug user (alcohol and heroin). Ketamine, ecstasy and methamphetamine were commonly used	Baseline survey: July 2009-January 2010 Follow-up: NA Methods: Audit of cases of GBL dependence Measure(s): History of drug use, prior withdrawal, social functioning, reasons for using GBL, and adverse effects of GBL use Potential confounders/covariates: NA	Patients reported impaired social functioning associated with GBL dependence and difficulty in accessing treatment. Nineteen patients underwent detoxification and 16 completed withdrawal. One patient developed delirium and required transfer to the in-patient detoxification unit. The majority of patients had persisting insomnia, anxiety and depression for weeks after withdrawal
Degenhardt et al., (2003)[51] Australia Cross-sectional study	76 participants who had used GHB in the previous 6 months Sex: 79% male Age: mean 27 years Ethnicity: NR Substance use: participants also used a variety of other drugs including cannabis, ecstasy, alcohol, methamphetamine, amphetamine, MDA, LSD, Ketamine, cocaine, heroin and other opioids, tobacco, Viagra, benzodiazepines, amyl nitrate	Baseline survey: January-June 2001 Follow-up: NA Methods: Association between GHB use and overdose examined Measure(s): Incidence of GHB overdose Potential confounders/covariates: NA	53% participants had overdosed on GHB. Those who had overdosed had on average used GHB for longer and on more occasions and were more likely to nominate GHB as their favourite drug
Kim et al., (2007)[52] USA Cross-sectional study	131 GHB users older than 16 years Sex: 70% male Age: mean 31 years Ethnicity: White non-Hispanic (71.8%); others 2(8.2%) Substance use: GHB (100%); tobacco use current (46.6%)	Baseline survey: January 2003-July 2006 Follow-up: NA Methods: High risk behaviours and hospitalisation for GHB intoxication Measure(s): Risky behaviours: engaging in sex; co ingestion of ethanol, ecstasy, ketamine; lifetime use of GHB >20 times; use of GHB while alone; driving; use of GHB to treat symptoms; use of heroin ever; use of a GHB precursor or analogue Potential confounders/covariates: NR	Increased risk of GHB hospital treatment was associated with: co-ingestion of ethanol; driving under the influence of GHB; use of GHB to treat withdrawal symptoms, and co-ingestion of ketamine

8. Novel synthetic drugs

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Wilkins & Sweetsur (2010)[53] New Zealand Cross-sectional study	National household survey of BZP/TFMPP use among resident population aged 13-45 years (n=2,010); analysis included only those reporting BZP/TFMPP use at least once in the previous 12 months (n= 293) Sex: 60% male Age: mean 24 years Ethnicity: 19% Maori Substance use: past year users	Baseline survey: February-March 2006 Follow-up: NA Methods: Structured questionnaire concerning BZP and other drug use and related harms Measure(s): Prevalence of party pill use, Drug types used in combination with party pills, Number of party pills used, Harm in areas of life, Physical and psychological problems, Milligrams of BZP/TFMPP used Potential confounders/covariates: NR	Most frequent harms experienced were insomnia (50%), headaches (22%), nausea (22%), tremors and shakes (19%), dizziness (15%) and heart palpitations (15%). Less commonly reported harms experienced were shortness of breath (11%), confusion (12%), vomiting (12%), short temper (11%), anxiety (10%), visual hallucinations (9%), depression (8%), inability to urinate (10%), paranoia (8%), auditory hallucinations (7%), blurred vision (6%), and chest pains (4%)
Wilkins et al., (2007)[54] New Zealand Cross-sectional study	National household survey of BZP/TFMPP use among random sample of 2,010 people (13-45 years old) Sex: 60% male Age: mean 24 years Ethnicity: 76.2% of users were European Substance use: 25% had ever used BZP/ TFMPP; 15% had used BZP/TFMPP in the last year	Baseline survey: February-March 2006 Follow-up: no follow up – looks at the previous 12 months Methods: Structured questionnaire concerning BZP and other drug use and related harms Measure(s): Patterns of use, Dependency, General harms, Adverse physical and psychological symptoms, Accessing health services. Potential confounders/covariates: NR	General areas of life most commonly harmed by BZP/TFMPP use were 'energy and vitality' (19.3%; 95% CI 14.8-24.8%), 'health' (14.6%; 95% CI 10.6-19.9) and 'financial position' (8.8%; 95% CI 5.7-13.4%); 33% of last year users had experienced harm from legal party pill use in at least one of the areas of life asked about. Physical problems most commonly experienced by users from legal party pill use were 'insomnia' (50.4%; 95% CI 44.1-56.7%), 'poor appetite' (41.1%; 95% CI 35.0-47.4%), 'hot/cold flushes' (30.6%; 95% CI 25.0-36.9%), 'heavy sweating' (23.4%; 95% CI 18.4-29.3%), 'stomach pains/nausea' (22.2%; 95% CI 17.4-28.0%) and 'headaches' (21.9%; 95% CI 17.2-27.4%). A small numbers of legal party pill users reported 'fainting/ passing out' (n=54) or 'fits/seizures' (n=51). Those experiencing physical problems reported an average of five physical symptoms in the last year (median 4, range 1-20 symptoms). Psychological problems most commonly reported by users were 'strange thoughts', 'mood swings', 'confusion', and 'irritability'. Only small numbers reported 'feelings of aggression' (n=56) or experienced 'suicidal thoughts' (n=52)
Wilkins et al., (2008)[55] New Zealand Cross-sectional study	189 participants (13-45 years) who used BZP/TFMPP Sex: 60% male Age: mean 23 years Ethnicity: 75% European; 20% Maori; 3% Asian; 1% Pacific Islander Substance use: mean number BZP/TFMPP taken on an occasion of greatest use=3.9 pills; mean quantity of BZP/TFMPP taken on an occasion of greatest use=533 mg 89% had used other drugs at the same time: alcohol (91%); tobacco (37%); cannabis (21%); 5-HTP pills (9%)	Baseline survey: NR Follow-up: NA Methods: interviews, harms Measure(s): patterns of use; other drugs used in combination; physical and psychological symptoms Potential confounders/covariates: NR	Being female, using cannabis and other drugs concurrently with BZP/TFMPP pills, taking large quantities of BZP/TMFPP pills in a single session and taking 5-hydroxytryptophan (5-HTP) recovery pills at the same time as party pills were independent predictors of having experienced an adverse problem from party pills. Physical problems from BZP/TFMPP pills reported most often by the sample were insomnia (54%), headaches (26%) and nausea (21%). Lower proportions of the sample experienced heart palpitations (18%), dizziness (15%), vomiting (13%) and chest pains (4%). Only very small numbers of users reported passing out (3%) and seizures (0.4%)

9. Opioids (illicit and prescription)

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Backmund et al., (2009)[56] Germany Cross-sectional study	1,049 patients (16-54 years) analysed on admission for opioid detoxification. All participants met the criteria for opioid dependency Sex: 65% male Age: mean 28 years Ethnicity: NR Substance use: participants average length of opioid use was 10 years	Baseline survey: NR Follow-up: NA Methods: interview Measure(s): emergency room treatment and overdose Potential confounders/covariates: age at first use, mental health, other drug use	More than a third of patients (34.7%) reported having ever experienced hospitalisation due to heroin overdose. Daily use of barbiturates and cannabis were independently associated with emergency room treatment
Burns et al., (2004)[57] Australia Cross-sectional study	163 heroin users (15-30 years) recruited from three General Practices, 42% of whom had ever overdosed requiring an ambulance or naxolone Sex: 54% male Age: median 21 years Ethnicity: NR Substance use: heroin (100%); prescriptions for opioids and benzodiazepines (NR)	Baseline survey: NR Follow-up: NA Methods: Linkage of data on use of Pharmaceutical Benefits Scheme (PBS) prescription drugs with data from a self-report questionnaire Measure(s): Mental Health: Beck Hopelessness Scale; Short Mood and Feeling Questionnaire; BRASH brief scale measuring self-harm; anti-social behaviour. Mental illness diagnosis. Use of prescribed drugs. Potential confounders/covariates: age, employment status, mental health	Prescriptions of benzodiazepines, opioids and anti-depressants were all significantly associated with heroin overdose. Young people using heroin reported high rates of feelings of hopelessness, depression, antisocial behaviour, self-harm and diagnosed mental illness
Catalano et al., (2011)[58] USA Raising Healthy Children Cohort study	1,040 participants from 1st and 2nd grade students recruited to the Raising Healthy Children study who had reported on use of non-medical prescription opiates (NMPOs). Drug use was monitored from 10th grade (mean age 16.3 years) to age 21; 912 participants followed up at age 21 (88%) Sex: 53% male Age: mean 16.3 years Ethnicity: 82% White; 5% Hispanic; 7% Asian or Pacific Islander; 5% Black; 3% Native American Substance use: Use of other drugs was very common among NMPO users particularly heavy users. Alcohol, cannabis and tobacco were very commonly used	Baseline survey: 10th grade Follow-up: to age 21 Methods: self-report questionnaire and interview Measure(s): CIDI Composite International Diagnostic Interview - substance use and other mental health disorders. Substance use measured through self-report. Potential confounders/covariates: gender, alcohol, cigarette, cannabis, other drugs	NMPO use predicted violent behaviour at age 21. Effects on mood disorder, property crime, and no school or work, which were significant when analysed separately for NMPOs or other hard drugs, were not significant when both were in the same model
Hickman et al., (2003)[59] UK Cohort study	881 problem drug users with main problem drug of heroin Sex: 74% male Age: mean 28 years Ethnicity: 75% White; 2% Black; 4% Indian/Pakistani; 19% missing Substance use: 76% injecting drug users	Baseline survey: records from 1997-1999 on the Drug Misuse Database Follow-up: NA Methods: mortality rate calculated and compared to control sample from London in 1999 Measure(s): mortality rate Potential confounders/covariates:	Mortality was 17 times higher in male and female heroin users compared to the control population. In the sample, mortality was higher among males, users older than 30 years and injectors but not significantly higher

9. Opioids (illicit and prescription)

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Jovanovic-Cupic et al., (2006)[60] Serbia Cohort study	57 drug users and tramadol addicts (16-43 years) recruited at the Institute for Addiction during 2002 Sex: 82% male Age: mean 22 years Ethnicity: NR Substance use: 17.5% used tramadol alone. 82.5% used tramadol along with other drugs including heroin, alcohol, benzodiazepine	Baseline survey: 2002 Follow-up: over first 12 months of treatment Methods: association between seizure frequency and drug use examined Measure(s): seizure diagnosis Potential confounders/covariates: other drug use	Among 57 patients, 31 had evidence for generalized tonic/clonic seizures. Seizures were multiple in 55% cases, and occurred in 85% cases <24 h after tramadol intake. Seizures were more common in those with a longer exposure to tramadol. Intake of tramadol with alcohol resulted in seizure occurrence at a lower dose than with other combinations
Mirakbari et al., (2003)[61] Canada Case-control study	1,155 participants with acute opioid overdose who received naloxone in the prehospital or emergency department setting because of presumed opioid overdose; 58 (5%) had taken pure opioid overdoses; 922 (80%) co-administered alcohol, cocaine or CNS depressant drugs; 175 (15%) unclear Sex: 88% male Age: mean 33-36 years Ethnicity: NR Substance use: see participant details	Baseline survey: 1997-1999 Follow-up: NA Methods: hospitalisation or outcome events examined Measure(s): telephone interview to identify hospitalisation or outcome events in the 24 hours after enrolment Potential confounders/covariates: co-morbid illness, other drug use, systolic BP, Diastolic BP, respiratory rate, temperature, heart rate	This study suggests that co-intoxicants do not increase the risk of short-term adverse events in survivors of opioid overdose. This study failed to identify drug combinations that identify patients at higher or lower risk
Smyth et al., (2007)[62] USA Cohort study	581 participants admitted during 1962-1964 to the California Civil Addict Program Sex: 100% male Age: mean 25 years Ethnicity: Hispanic (55.6%); White (36.5%); African American (7.9%) Substance use: heroin	Baseline survey: 1962-1964 Follow-up: 33 years Methods: years of potential life lost calculated Measure(s): age at time of death; cause of death Potential confounders/covariates:	The leading cause of death was heroin overdose followed by chronic liver disease. On average, addicts in this cohort lost 18.3 years of potential life before age 65. In total 22.3% of the years lost was due to heroin overdose, 14.0% due to chronic liver disease, and 10.2% to accidents. The total years of potential life lost was significantly higher than in the overall US population. Within the cohort, premature mortality was significantly higher in Whites and Hispanics than African American addicts

10. Khat and salvia divinorum

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Baggott et al., (2010)[63] USA Cross-sectional study	500 participants (13-68 years) recruited from a drug information website Sex: 93% male Age: mean 23 years Ethnicity: NR Substance use: Participants had used salvia a median 6 times and 80.6% probably or definitely would use SD again	Baseline survey: July-August 2003 Follow-up: NA Methods: self-report questionnaire Measure(s): reports of positive and negative effects lasting 24 hours or more; effects experienced; addiction rates Potential confounders/covariates:	Reported effects included: increased insight (47%), improved mood (45%), calmness (42%), increased connection with universe or nature (40%), weird thoughts (36.4%), floating feeling (32%), increased sweating (28%), body feeling warm (25%), mind racing (23%), lightheadedness (22%) things seeming unreal, drowsiness (19%) 4.4% reported persisting negative effects for over 24 hours, most often anxiety. 25% reported persisting positive effects

11. Polystubstance use

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Pérez et al., (2009)[64] Spain Cross-sectional study	1,579 patients (18 years or over) who were admitted to a trauma emergency department with a traumatic injury sustained within the previous 6 hours Sex: 56% male Age: NR Ethnicity: NR Substance use: mixed	Baseline survey: October 2005, March 2006 and July 2006 Follow-up: NA Methods: interview and oral fluid specimen or sweat sample Measure(s): presence of alcohol, any illegal substance (e.g. cannabinoids, cocaine, MDMA, opiates), and other psychostimulant drugs (e.g. benzodiazepines) Potential confounders/covariates: gender, age, educational level, occupation, transportation to hospital, form of discharge, and severity of the injury	Alcohol was the most frequently detected substance (n=270); cannabinoids were the most frequently detected illegal substance followed by cocaine (n=355 and n=189, respectively). Prevalence of ecstasy and opiates was <1% in all groups. Prevalence of benzodiazepines was 1% or lower. The prevalence of substances detected was much higher among patients who suffered a violent injury than for other circumstances. Overall, 26.4% of men and 10.7% of women injured in a violent episode were positive for any illegal substance
Mazzoncini et al., (2010)[65] UK Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study Cross-sectional study	468 patients (16-64 years) presenting to secondary services with a first episode of psychosis (FEP) according to ICD-10 criteria Sex: NR Age: NR Ethnicity: NR Substance use: any drug use 45%; cannabis 42%; amphetamines 12%; hallucinogens 9%; cocaine 8%; opiates 3.5%; barbiturates 1%; other 1.5%	Baseline survey: 1997-1999 Follow-up: NA Methods: interview, review of case notes Measure(s): Schedules for Clinical Assessment in Neuropsychiatry; a modified Personal and Psychiatric History Schedule (PPHS); Schedule for Drug Use Assessment (SDUA) Potential confounders/covariates: age, gender, ethnicity, study centre, diagnosis, who the patient lived with, accommodation type, relationship status, level of education, employment status, mode of contact and mode of illness onset	FEP patients used three to five times more substances compared to a general population sample from the BCS. Any drug use was associated with poorer social adjustment (including unemployment and living in a non-self owned property) and a more acute mode of onset. Cannabis use did not affect social adjustment, but was associated with a more acute mode of onset
Coghlan & Macdonald (2010)[66] Australia Cross-sectional study	1,021 participants in treatment for various addictions including a primary problem for cocaine (n=300), cannabis (n=128), alcohol (n=110), other drugs (n=35), tobacco (n=249) or gambling (n=199) Sex: 55% male Age: NR Ethnicity: NR Substance use: see participant details	Baseline survey: February 2003-July 2006 Follow-up: NA Methods: self-administered questionnaire Measure(s): frequency of all injury events during the past 12 months for which they received medical treatment; places where the injuries happened; timing and cause of the most recent injury event; nature of the injury; restriction of activity; hospitalization that resulted from the injury; whether had consumed cannabis, cocaine, alcohol, or other drugs in the 6-hour period before the most recent incident; frequency of substance use Potential confounders/covariates: psychosocial variables	Clients in treatment for cocaine were most likely to report an incident of injury (36%), while the other groups were substantially lower: cannabis (15%), alcohol (13%), tobacco (18%), and gambling (13%). Both frequency of cocaine and cannabis use, risk-taking/impulsivity, stress, and coping were significantly related to injuries. For the multivariate analyses, only risk-taking /impulsivity, stress, age, and sex were significantly related to injuries

11. Polystubstance use

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Caspers et al., (2009)[67] USA Cohort study	1,235 middle-aged adult adoptees; 25% followed up at 5 years Sex: 42% male Age: mean 44 years Ethnicity: 94% White; 2% African American; 4% Hispanic or other Substance use: cannabis, tobacco, alcohol commonly used	Baseline survey: 1999-2003 Follow-up: 5 years Methods: semi-structured assessment Measure(s): DSM-IV diagnostic interview; health service utilisation; health problems Potential confounders/covariates:	Lifetime diagnoses of cannabis and other non-cannabis substance misuse significantly predicted new occurrences of cardiovascular and metabolic disease. Alcohol misuse predicted earlier onset of cardiovascular disease among men. Cannabis and other non-cannabis drugs predicted earlier onset of cardiovascular disease for men and women. Cannabis and other non-cannabis drugs predicted earlier onset of metabolic disease among men
Ahlm et al., (2009)[68] Sweden Cohort study	200 fatally and non-fatally hospitalised drivers; 56 fatally and 144 non-fatally injured drivers Sex: fatal=89% male; non-fatal = 71% male Age: fatal=mean 42 years; non-fatal=mean 36 years Ethnicity: NR Substance use: tested postitive for - Alcohol, benzodiazepines, opiates/ analgesics, and antidepressants, amphetamine, THC, testosterone, epestosterone, and nandrolone	Baseline survey: 2005-2007 Follow-up: NA Methods: blood and urine analysis Measure(s): injuries classified according to the Abbreviated Injury Scale Potential confounders/covariates: NR	38% of the fatally injured drivers tested positive for alcohol and of the non-fatally drivers, 21% tested positive. 7% and 13%, of fatally and non-fatally injured drivers, respectively, tested positive for pharmaceuticals with a warning for impaired driving, including most frequently benzodiazepines, opiates, and antidepressants. 9% of fatally injured and 4% of non-fatally injured drivers, respectively, tested positive for illicit drugs; tetrahydrocannabiol (THC) was the most frequently detected illicit substance
Blondell et al., (2005)[69] USA Cross-sectional study	887 patients (14 to 97 years) admitted to hospital through a trauma service Sex*: 70 % male Age*: mean 40 years Ethnicity*: 82% White; 13% Black; 1% Hispanic; 0.4% Asian; 4% other Substance use: positive test for: opiates 19%; cannabis 15%; benzodiazepines 12%; cocaine 7%; other drugs 4% *included patients excluded from study	Baseline survey: throughout 2001 Follow-up: NA Methods: drug tests and injury type Measure(s): alcohol and drug testing; injury type Potential confounders/covariates:	Cocaine was independently associated with violence-related injury and opioids were independently associated with nonviolent injuries and burns. Positive test results for any drug were not associated with any specific injury type. Patients with positive alcohol toxicology results were more likely to have violence-related and penetrating injuries than patients with negative results after adjustment for positive cocaine toxicology results, the association between alcohol and penetrating injury was no longer significant
Kertesz et al., (2007)[70] USA Coronary Artery Risk Development in Young Adults (CARDIA) Study Cohort study	5,115 adults (18-30 years); n=3124 followed up 15 years later Sex: 45% male Age: mean 27.2 years Ethnicity: 56% White; 44% Black Substance use: cannabis, cocaine, amphetamines, and opiates	Baseline survey: 1985-1986 Follow-up: 15 years Methods: Measure(s): self-report drug use (use of cannabis, cocaine, amphetamines, and opiates); general self-reported health (GSRH). Potential confounders/covariates: age, sex, race, socioeconomic status, current smoking, 'risky drinking', marital status, BMI, physical activity over 12 months, chronic medical conditions, social support, history of ever having been diagnosed with mental illness or a nervous disorder and family risk score	At follow-up, 7.3% of the sample reported a decline to Poor or Fair general health status. Decline was significantly more frequent among Current Hard Drug Users (12.6%) compared to three other categories of drug use: current cannabis use only (7.0%), past use (6.5%) and never use (7.2%). After accounting for potential covariates, participants who reported Current Hard Drug Users in 1987-88 reported a significant health decline over a 15-year period compared with those who were reported as Never Users in 1987/88 (odds ratio: 1.83; 95% CI 1.07, 3.12). Continued tobacco smoking was found to independently predict health decline and partly explained the association between young adult hard drug use and subsequent health decline. Neither current marijuana use (in 1987-88) nor past drug use were associated with general health decline

11. Polystubstance use

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Bartu et al., (2004)[71] Australia Cohort study (retrospective)	4,280 drug using individuals; n=2,887 opiate users and n=1,393 amphetamine users, admitted to hospital or psychiatric institutions in Perth for a condition or external cause related to opiate or amphetamine use. Sex: 53% male Age: mean 28.7 years Ethnicity: NR Substance use: see participant details	Baseline survey: 1985-1998 Follow-up: 1985-1998 Methods: association between mortality, drug treatment status and drug use examined Measure(s): age at time of death Potential confounders/covariates:	Opiate users were at 1.4 times the hazard of all-cause death and 2.4 times the hazard of drug-cause death compared with amphetamine users. Males were at 1.79 times the hazard of all-cause death and at 2.69 times the hazard of drug-cause death compared with females. Clients in drug treatment had a lower hazard of death compared with non-clients and those who had ceased treatment. Participants who had ceased treatment more than 6 months ago had 7.0 times the hazard of all-cause death and 8.4 times the hazard of drug-cause death
Martins et al., (2007)[72] USA Cross-sectional study	1,118 trauma centre patients (18-96 years) admitted due to motor vehicle accident, gunshot injury, knife injury, beating or other injury Sex: 72% male Age: mean 37 years Ethnicity: 56.3% White; non-White 43.7% Substance use: 79% reported lifetime use of at least one substance; 34% alcohol only; 7.6% only illegal drugs; 37.7% alcohol and drug use	Baseline survey: NR Follow-up: NA Methods: addiction and hospital admission Measure(s): addiction risk Potential confounders/covariates:	Trauma inpatients had a higher absolute addictive risk than the general population, comparable to the risk found in patients in treatment for substance use disorders
Georgiades & Boyle (2007)[73] Canada Ontario Child Health Study Cohort study	2,381 individuals (12-16 years) who took part in the Ontario Child Health Study; 1,286 were followed up at 18-21 years (54%) Sex: ~50% male Age: 12-16 years Ethnicity: NR Substance use: tobacco and cannabis use reported	Baseline survey: 1983, 1985 and 1987 Follow-up: at age 18 to 21 Methods: tobacco and cannabis use in adolescence and adulthood examined with physical and mental health Measure(s): adolescent survey: tobacco use for 30 continuous days; past 6-month cannabis use; general health status (RAND Health Insurance Study); externalizing and internalizing syndrome scales (Ontario Child Health Study-Revised); chronic illness/medical condition Adult survey: physical health (Short Form-36 Physical Healthy Survey); life satisfaction; 12 month prevalence of major depressive disorder; past year cannabis use; daily tobacco use for 30 continuous day; Potential confounders/covariates:	Adolescent tobacco use but not cannabis use is associated with lower general health and physical health. Both tobacco and cannabis use was significantly related to having major depressive disorder, lower life satisfaction and less years spent in education. Adults who used tobacco only in adolescence are at greater risk of poor physical health. Adults who used tobacco in adolescence and adulthood are at greater risk on physical health, life satisfaction and of developing a major depressive disorder. Use of cannabis in adulthood, and continued use from adolescence into adulthood, was associated with lower life satisfaction and an increased risk for major depressive disorder. For adults who only used cannabis in adolescence, use was not associated with health outcomes

11. Polystubstance use

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Spinks et al., (2007)[74] USA Iowa Adoptions Study Cohort study	742 adoptees interviewed in the most recent wave of the Iowa Adoptions Study were examined in 3 groups; n=467 no abuse, n=251 alcohol users, and n=191 alcohol and drug users Sex: 37-65% male across groups Age: mean 40-42 years across groups Ethnicity: NR Substance use: subjects in all three groups may have used other substances but did not reach diagnostic criteria for either abuse or dependence of these substances at any point in their lives	Baseline survey: NR Follow-up: NA Methods: interview Measure(s): incidence of: cardiovascular disease, metabolic disease, organic brain disease, any type of STD, traumatic brain injury, death. Age of diagnosis of systemic disease. Potential confounders/covariates: age, education, tobacco use, gender, heaviest lifetime alcohol use, presence or absence of illicit drug use	Using both alcohol and drugs was significantly associated with having died at the time of last follow-up. Substance abuse/dependence did not predict the incidence of cardiovascular disease, (however heavier alcohol use in males inferred an increased risk of cardiovascular disease) or metabolic disease. After controlling for covariates there was no effect of group or level of substance exposure on the incidence rate of organic brain disease or STDs or traumatic brain injury
Borders et al., (2009)[75] USA Cohort study	706 participants (18 years or older), who had used crack or powder cocaine and/or methamphetamine by any route of administration in the past 30 days; 79% followed-up at the 24-month interview Sex: 61% male Age: mean 33 years Ethnicity: 66% White, 32% African American, 3% other Substance use in past 30 days: 59% crack cocaine; 48% powder cocaine; 43% methamphetamine	Baseline survey: Follow-up: 2 years Methods: interviews using computer-assisted personal interview (CAPI) technology. Measure(s): alcohol, drug use (Addiction Severity Index) psychiatry severity, and physical health-related quality of life (SF-8) Potential confounders/covariates: age of first substance use, demographics, social and economic factors, medical care access indicators, and physical health problems	Over the follow-up period, physical health related quality of life scores did not change but ASI-drug, alcohol and psychiatric scores improved significantly over time. Higher (i.e. worse) drug severity was associated with lower (i.e. worse) scores on the measure of physical health-related quality of life

12. Cross-cutting themes

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Boys & Marsden (2003)76 UK Cross-sectional study	364 polydrug users (16-22 years) who used at least two of cocaine, ecstasy, cannabis and amphetamines on five or more separate occasions during the past 90 days Sex: 56% male Age: mean 19.3 years Ethnicity: NR Substance use: 90% alcohol; 96% cannabis; 52% amphetamines; 49% ecstasy; 26% LSD; 51% cocaine powder	Baseline survey: NR Follow-up: NA Methods: clinical interview Measure(s): Maudsley Addiction Profile; ICD-10 and DSM-IV; negative effects (using a stronger dose than intended; using more of a substance than intended; risky behaviour after using a substance; feeling anxious or nervous after using a substance), substance use functions, perceived peer substance misuse measured through self-report. Potential confounders/covariates:	Scores on the negative mood function and social function increased with higher intensity of use of alcohol, cannabis, ecstasy, amphetamines and cocaine, but scores were judged likely to be explained by other variables measured. Experiencing negative effects were associated with cannabis, ecstasy, amphetamine and cocaine use
Galea et al., (2006)77 USA Cross-sectional study	1,066 habitual drug users in New York City including in the past year 99% who had used heroin and 87% had used cocaine. 78% heroin users and 79% cocaine users were severely dependent on that drug. Sex: heroin user: 75% male; cocaine user 77% male Age: heroin users: 62% aged 35+; cocaine users: 61% aged 35+ Ethnicity: heroin user/cocaine user. Black (23%/28%); Hispanic (65%/60%); White (13%; 13%) Substance use: see participant details	Baseline survey: NR Follow-up: NA Methods: association between heroin and cocaine dependence and overdose examined Measure(s): heroin and cocaine dependence level; rate of overdose Potential confounders/covariates: length using drug, injection status, use of other drugs	Participants who were severely heroin dependent were less likely to have overdosed on any drug in the past year. Participants who were severely cocaine dependent were more likely to have overdosed in the past year
Phillips & Stein (2010)78 USA Cross-sectional study	51 participants (at least 18 years old), had injected drugs within the last month but were not experiencing psychotic symptoms Sex: 67% male Age: mean 39.2 years Ethnicity: 88% White, 8% Hispanic/ Latino, 2% Asian/Pacific Islander, 2% Native American Substance use: heroin, methamphetamine or speedball primary drug of choice; mean 17.9 years of injection	Baseline survey: November 2007-August 2008 Follow-up: NA Methods: structured interview Measure(s): drug use and injection history, and history of bacterial infections. Potential confounders/covariates: hand washing, intramuscular injection, and days of heroin injection in last month	Participants with a skin infection were more likely to inject intramuscularly (OR 1.57; 95% CI 0.90-2.69) and reported greater days of heroin injection in the last month (OR 1.08; 95% CI 1.01-1.16) compared to those with no history of skin infections in the last year. Injectors with a past history of skin infections who reported heroin or speedball as their drug of choice self-reported a significantly higher number of past skin infections (mean 3.6, corresponding to 4–6 skin infections, SD=1.57) compared to methamphetamine and cocaine users (mean 1.9, corresponding to 1–2 skin infections, SD=0.69) (p=0.01 for comparison)

12. Cross-cutting themes

STUDY	STUDY POPULATION	DATA COLLECTION	RESULTS
Talamini et al., (2010)[79] Italy Case-control study	326 patients (34-80 years) with incident pancreatic cancer admitted to hospitals in the greater Milan area; matched control group included 652 patients admitted for acute conditions to the same hospital; Sex: 53% males Age: median 63 years (range 34-80 years) Ethnicity: NR Substance use: group included never smokers (n=137), former smokers (n=88) and current smokers (n=100) and never drinkers (n=44), former drinkers (n=28) and current drinkers (n=254	Baseline survey: 1991-2008 Follow-up: NA Methods: structured questionnaire Measure(s): sociodemographic factors and lifestyle habits including alcohol and tobacco use, family history of cancer, diet, problem orientated medical history, Potential confounders/covariates: year of interview, education, self-reported history of diabetes mellitus, BMI, drinking and smoking habits	Pancreatic cancer was associated with current smoking (odds ratio 1.68; 95% CI 1.13–2.48) and the risk rose with increasing number of cigarettes/day (≥20 cigarettes/day odds ratio 2.04; 95% CI 1.14–3.66). No association emerged for former smokers. Alcohol consumption was associated with increased pancreatic cancer risk (OR 1.44; 95% CI 0.92–2.27), but significant only among heavy drinkers consuming ≥21 drinks/week (≥35 drinks/week OR 3.42; 95% CI 1.79-6.55). Pancreatic cancer risk was higher in heavy smokers (≥20 cigarettes/day) and heavy drinkers (≥21 drinks/week) in comparison with never smokers who drunk <7 drinks/week (OR 4.29; 95% CI 1.93–9.56)
Tyndall et al., (2003)[80] Canada Vancouver Injection Drug Users Study (VIDUS) Cohort study	1,126 VIDUS participants including 109 HIV seroconversion participants (mean age 33.6 years) and 831 HIV negative participants (mean age 34.5). Of 109 HIV seroconversion participants, 62% injected cocaine in the past week, 35% injected heroin in the past week and 6% used crack cocaine in the past week. For the 831 HIV negative participants, 39% injected heroin, 46% injected heroin and 11% used crack cocaine.; n=940 (83%) Sex: ~66% male Age: mean age approx 34 Ethnicity: ~25% aboriginal Substance use: see participant details	Baseline survey: May 1996 Follow-up: mean 31 months Methods: A Kaplan–Meier analysis of the time to HIV seroconversion was performed according to drug use frequency Measure(s): Potential confounders/covariates: adjusted for analysis	Risk of HIV seroconversion directly related to intensity of injection cocaine use. Injection of heroin alone was not significantly related to HIV seroconversion

PART THREE
SUMMARY OF CASE REPORTS

13. Ketamine

STUDY	STUDY POP'N	CASE DETAILS	SUBSTANCE	ADVERSE EVENTS
Chu et al., (2008)[81] Hong Kong	N=59	All patients (38 men and 21 women, mean 24.3 years) had severe LUTS, with frequency, urgency, dysuria, urge incontinence and occasional painful haematuria	Patients had documented regular ketamine use ≥3 months (mean 3.5 years of use)	Cystoscopy showed various degrees of inflammation similar to chronic interstitial cystitis in 42 (71%) patients
Cottrell et al., (2008)[82] UK	N=9	Nine patients presenting with symptoms of severe urinary frequency, urgency, macroscopic haematuria, and suprapubic pain	All case reported a history of chronic ketamine use	Cystoscopy showed a contracted shrunken bladder with erythema and contact bleeding. Complications included hydronephrosis and renal impairment
Shahani et al., (2007)[83] Canada	N=9	Patients presented with severe dysuria, frequency, urgency, and gross haematuria	All patients were daily ketamine users	Computed tomography revealed marked thickening of the bladder wall, a small capacity, and perivesicular stranding, consistent with severe inflammation. All patients had severe ulcerative cystitis on cystoscopy

14. Serotonergic hallucinogens

STUDY	STUDY POP'N	CASE DETAILS	SUBSTANCE	ADVERSE EVENTS
Bickel et al., (2005)[84] Germany	N=1	25-year-old man infected with hepatitis C with a history of drug and alcohol abuse presented with abdominal pain and vomiting, agitation, aggression and hallucinations	Had used magic mushrooms	Severe rhabdomyolysis and acute renal failure, and later developed posterior encephalopathy with cortical blindness
McClintock et al., (2008)[85] USA	N=1	28-year-old man with a history of drug and alcohol abuse presented multiple times to the hospital over 2 months with an elusive constellation of symptoms, resolving spontaneously in each instance	Toxic mushrooms ingestion (later admitted to using these)	Experienced vomiting, strange behaviour, diaphoretic, dilated pupils, euphoria
Nielen et al., (2004)[86] The Netherlands	N=2	Two males aged 33 and 35 years old, suffering from psychotic symptoms. Both patients had a history of schizophrenic symptomatology	One patient used cannabis and psilocybin containing mushrooms, had recently changed the type of mushrooms used, second patient used psilocybin containing mushrooms only	Psychotic state

15. Novel synthetic drugs

STUDY	STUDY POP'N	CASE DETAILS	SUBSTANCE	ADVERSE EVENTS
Alatrash et al., (2006)[87] USA	N=1	23-year-old man presented with combative behaviour and hallucinations	Had ingested 25 mg of 5-MeO-DIPT 30 minutes before symptom onset	Hypertension, tachycardia and fast breathing rate; rhabdomyolysis and transient acute renal failure diagnosed
Ambrose et al., (2010)[88] USA	N=1	43-year-old woman with severe headaches coupled with confusion	Had taken liquid form of 2C-B, 48 hours before	Progressive encephalopathy and quadraparesis
Austin et al., (2004)[89] New Zealand	N=1	20-year-old man with no history of psychotic disorders	Had consumed 4 tablets of 'Rapture', plus nitrous oxide and small amount of cannabis. Tested positive for BZP	Experienced an acute psychotic episode with verbal and auditory hallucinations and disillusional beliefs
Drees et al., (2009)[90] USA	N=1	39-year-old African-American woman presenting with rapidly diminishing mental status, hypertension, vasoconstriction	History of alcohol, cocaine, MDMA, and 2C-I ingestion. Screening identified MDA and 2C-I	Haemorrhagic stroke and underlying Moyamoya disease diagnosed
Gee et al., (2010)[91] New Zealand	N=2	Case 1. 19-year-old female with history of schizophrenia and substance abuse taken to police custody after being found in a confused state; Case 2. 22-year-old male who collapsed at a party	Case 1. BZP; Case 2. 3-4 'party pills' containing BZP	Case 1 experienced confused mental state; seizure; generalised tonic-clonic activity; Case 2 experienced collapse; brief seizure; hyperthermia; hypoglycaemia; metabloic acidosis; coagulopathy; rhabdomyolysis; acute kidney injury; and hypertension
Kovaleva et al., (2008)[92] Belgium	N=1	Female patient complaining of nausea and drowsiness	Took 3 tablets which contained mCPP. Had used cocaine and alcohol. Amphetamine, benzoylecgonine (primary metabolite of cocaine) and detected in tablets	Experienced symptoms of agitation, anxiety, drowsiness, flushing, visual disturbances, and tachycardia
Meatherall & Sharma (2003)[93] Canada	N=1	21-year-old white male presented feeling 'weird'	Ingested a 'Foxy' tablet; confirmed to be 5-MeO-DIPT	Visual hallucinations and could not move limbs; fast heart rate and breathing on examination but no motor sensory deficit
Miyajama et al., (2008)[94] Japan	N=1	40-year-old man, with no previous history of mental disorder, presenting in a delusional state with incoherent speech	2C-T-4 had been taken 9 hours earlier	Psychotic state
Ovaska et al., (2008)[95] UK	N= 1	20-year-old man with no significant past medical history collapsed having tonic-clonic seizures	DOI; alcohol use and other recreational drug use, including MDMA, was also reported. Substance confirmed as DOC (2,5-dimethoxy-4-chloroamphetamine)	Sinus tachycardia on admission, metabolic acidosis and biochemical evidence of rhabdomyolysis
Sammler et al., (2010)[96] UK	N= 1	15-year-old girl presented with altered mental status, nausea, and vomiting	Had consumed a white powdery substance together with alcohol. Analysis was consistent with mephedrone	Euvolaemic hypo-osmotic hyponatraemia with encephalopathy and raised intracranial pressure
Tanaka et al., (2006)[97] Japan	N=1	29-year-old male developed abnormal symptoms including very intense agitation	Partner had injected an aqueous solution of 5-MeO-DIPT into his anus	Died the day after admission to hospital; autopsy evidence of myocardial ischemia and pulmonary haemorrhage
Wilson et al., (2004)[98] USA	N=1	23-year-old white male presented with nausea and vomiting	Had a ingested a capsule of unknown contents; found to contain 5-MeO-DIPT	Sensory hallucinations, sensation of insects crawling on the skin and paranoia/anxiety
Wood et al., (2010)[99] UK	N= 1	22-year-old man developed palpitations, "blurred tunnel vision," chest pressure, sweating, and a feeling of being generally unwell	Ingested 200 mg of mephedrone orally, followed by intramuscular injection of 3.8 g diluted in sterile water	Sympathomimetic toxicity: anxious and agitated, fast heart rate, high blood pressure and dilated pupils

16. Nitrites

STUDY	STUDY POP'N	CASE DETAILS	SUBSTANCE	ADVERSE EVENTS
Graves et al., (2003)[100] UK	N=1	35-year-old Afro-Caribbean man. Patient had felt generally unwell with fevers. He had passed red urine and the white of his eyes had become yellow	Patient had been using cannabis daily and crack cocaine occasionally; 2 days before onset of symptoms he inhaled amyl nitrate	Haemolytic anaemia
Stalnikowicz et al., (2004)[101] Israel	N=3	Three patients (aged 19, 27 and 35) who presented with acute haemolysis after inhalation of butyl nitrite	All patients had inhaled poppers for recreational purposes and for intensifying sexual experience. One patient also abused heroin and smoked	Acute haemolytic anaemia was diagnosed in all 3 cases. Two patients had a genetic deficiency which predisposed them to non-immune haemolytic anaemia (GD6P deficiency)
Vignal-Clermont et al., (2010)[102] France	N= 4	Patients presenting with prolonged visual loss	Substance details: all cases had inhaled poppers with isopropyl nitrites identified	Cases experienced retinal damage

17. Khat and salvia divinorum

STUDY	STUDY POP'N	CASE DETAILS	SUBSTANCE	ADVERSE EVENTS
Breton et al., (2010)[103] France	N=1	17-year-old female with a history of mental health problems and cannabis use	Patient had smoked dried leaves of salvia divinorum	Derealisation and hallucinations; self-mutilation
Chapman et al., (2010)[104] UK	N=6	Six patients with a history of unexplained liver disease	All patients chewed khat	Cases experienced severe, acute hepatitis that resulted in death or liver transplantation
Corkery et al., (2010)[105] UK	N=13	Thirteen deaths in the UK occurring between 2004 and 2009	Deaths were associated with khat consumption	Reason for death were: liver failure (n=3); left ventricular failure and pulmonary oedema (n=1); arrhythmia (n=1); confirmed/ possible suicide (n=3); accidental overdose of an anti-psychotic (n=1); road accidents (n=2); and heroin intoxication (n=1)
Nielen et al., (2004)[86] The Netherlands	N=2	Two males aged 25 and 35 years old, suffering from psychotic symptoms including paranoid and aggressive behaviour	Both patients were chronic users of khat. One patients was also using alcohol	Psychotic state
Paulzen et al., (2008)[106] USA	N=1	18-year-old female patient admitted to psychiatric emergency service with acute onset of agitation, disorganisation, hallucinating behaviour and self-mutilating behaviour	Patient had smoked cannabis and unknowingly salvia divinorum	Subsequent decrease of alertness, developing toxic psychosis with stupor and catatonic excitement, potential neuroleptic associated elevation of creatine kinase and recurrent cardiac arrhythmias that required a temporary external cardiac pacemaker Later developed elevated temperature and hypotension, peritonitis and distended bowels
Przekup and Lee (2008)[107] USA	N=1	21-year-old man with no family or personal psychiatric history or laboratory abnormalities presented with acute psychosis and paranoia	Smoked salvia divinorum shortly before onset of symptoms	Patient demonstrated echolalia (automatic repetition of vocalisations made by another person), paranoia, flight of ideas, and psychomotor agitation
Singh et al., (2007)[108] USA	N=1	15-year-old male with a history of cannabis and salvia divinorum use. Presented with acute onset of mental status changes characterized by paranoia, déjà vu, blunted affect, thought blocking and slow speech of three days' duration	Patient had used cannabis prior to the onset of symptoms and had used salvia approximately 6 months earlier	Déjà vu remained as the main symptom while other symptoms subsided

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